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EXAMINER	
SHAFER, SHULAMITH H	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/562,081	VUOLTEENAHO ET AL.	
	Examiner	Art Unit	
	SHULAMITH H. SHAFER	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-21,23-37,40-44,46,47,49-52,59,60 and 62-68* is/are pending in the application.

4a) Of the above claim(s) *28-37 and 40-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-21,23-27,46,47,49-52,59,60 and 62-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

Applicants' amendment of 6 April 2010 is acknowledged. Claims 5, 6, 48, 53-58 and 61 are canceled. Claims 1-3, 9-12, 17-19, 21, 23, 24, 26, 27, 46, 47, 49-52, 59 and 60 are amended and the amendment made of record. Claims 62-68 are newly presented and have been entered.

Claims 1-4, 7-21, 23-37, 40-44, 46, 47, 49-52, 59, 60, and 62-68 are pending in the instant application. Claims 28-37 and 40-44 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. In the original response to requirement for election of species (Response of 10 July 2008), applicants elected the following species: SEQ ID NO:3 (NT-proANP), SEQ ID NO:6 (NT-proBNP), SEQ ID NO:9 (polynucleotide encoding SEQ ID NO:3), and SEQ ID NO:12 (polynucleotide encoding SEQ ID NO:6).

Claims 1-4, 7-21, 23-27, and 46-52, 59, 60, and 62-68 are under consideration to the extent they read on the elected invention.

Withdrawn Objections/Rejections

Claims 5, 6, 48, 53-58 and 61 are canceled; all objections and rejections of these claims are thereby moot.

Withdrawn Objections:

The objection to Claim 23 because of the claim contains a typographical error is withdrawn in light of applicants' amendment to the claim to recite "A polynucleotide comprising ***a*** sequence…".

Withdrawn Rejections:

The rejection of Claim 26 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is withdrawn in light of Applicants' amendment to the claim. Applicants have amended the claim to recite "An isolated host cell", thus obviating the rejection.

The rejection of Claim 1 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, is withdrawn in light of Applicants' amendment to the claim. Applicants have amended the claims to recite comparison of the detected levels to a reference level, thereby obviating the rejection.

The rejection of Claim 1 under 35 U.S.C. 112, second paragraph, as vague and indefinite in reciting "proportionally cumulative amount" is withdrawn in light of Applicants' amendment to the claim to delete recitation of "proportionally cumulative amount".

The rejection of Claim 17 under 35 U.S.C. 112, second paragraph, as vague and indefinite as failing to correlate changes in levels of pro-BNP and pro-ANP with heart failure or monitoring of treatment is withdrawn in light of Applicants' amendment to the claim. Applicants have amended the claim to recite "wherein detection of activation of the ANP and BNP hormonal systems is diagnostic of heart failure" and "detection of inactivation of ANP and BNP hormonal systems monitors successful treatment of a cardiac condition", thereby obviating the rejection.

The rejection of Claims 1-4, 7-17, 46, 47, 52, 59 and 60 under 35 U.S.C. 112, first paragraph, scope of enablement, is withdrawn in part, in light of Applicants' amendment to the claims. Issues still remaining are discussed below.

The rejection of Claims 1-4, 7-17, 46, 47, 52, 59 and 60 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn, in part, in light of Applicants' amendment to the claims. Issues still remaining are discussed below.

Maintained and/or New Objections and/or Rejections

Objections

Claims:

The objection to Claim 11 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is maintained. It is unclear how the recitation of "wherein the method comprises use of said fusion peptide" in the amended claim further limits Claim 3 which has been amended to recite "a fusion polypeptide agent or a fusion peptide agent".

Applicants assert (Remarks of 6 April 2010, page 27, last paragraph bridging page 28, 1st paragraph) that Claim 3 has been amended "to specify a "fusion polypeptide agent or a fusion peptide agent," rather than only a "fusion polypeptide agent." Claim 11 specifies that the method of claim 3 comprises use of a "fusion peptide agent," thus limiting the scope of claim". This is not persuasive; as will be discussed below, Applicants have not defined "fusion polypeptide agent" and "fusion peptide agent". One of ordinary skill would interpret these two phrases to have identical meaning. The objection is thus maintained.

Rejections

35 U.S.C. § 112, Second Paragraph:

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-4, 7-15, 18-21, 23-27, 46, 47, 49,51, 52, 59, 60, and 67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 3, 10, 12, 18, 19, 21, 23, 46, 47, 49, and 51 are vague and indefinite in reciting "a fusion polypeptide agent or a fusion peptide agent". These terms are not defined in the specification of the instant invention. Absent any limiting definitions in the specification, one of ordinary skill in the art would interpret the terms to refer to an identical fusion protein. Thus it is unclear what applicants intend by the recitation of both terms in the same claims.

Claims 2, 3, 46 and 47 are vague and indefinite. The claims recite a "first binding substance that is able to bind to:
(a) (i) proANP (SEQ ID NO:l), ANP (SEQ ID NO:2), or NT-proANP (SEQ ID NO:3....
(b) (i) proBNP (SEQ ID NO:4), BNP (SEQ ID NO:5), or NT-proBNP (SEQ ID NO:6); or
.....
(c) a fusion polypeptide agent or a fusion peptide agent comprising both (a) and (b)
(d) proANP (SEQ tD NO: 1), ANP (SEQ ID NO:2), or NT-proANP (SEQ ID NO:3); and
(e) proBNP (SEQ ID NO:4), BNP (SEQ ID NO:5), or NT-proBNP (SEQ ID NO:6).

It is unclear how sections (a) and (b) of the claims differ from sections (d) and (e) of the claims. Thus, it is unclear what applicants intend by the recited repetition in the claims.

The rejection of Claims 3 and 47, which depend from Claim 1, under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps is maintained for reasons of record and for reasons set forth below. See MPEP § 2172.01. Claim 1 is directed to a method of determining activation or inactivation of the atrial natriuretic peptide and brain natriuretic peptide hormonal systems by detecting the presence or amount of proANP and proBNP in a sample from the subject. Claims 3 and 47 recite contacting the sample with a fusion polypeptide agent or a fusion peptide agent comprising both proANP and pro-BNP and contacting the sample with a binding substance which is able to bind to pro-ANP and proBNP and a fusion polypeptide comprising both proANP and pro-BNP. The claims have been amended to recite "wherein said fusion polypeptide agent or said fusion peptide agent can be bound by a

first binding substance, and said fusion polypeptide agent or said fusion peptide agent is used as a calibration agent or a competitive inhibitor". However, the claims do not require the fusion polypeptide agent or fusion peptide agent to be labeled in any way that would allow one of ordinary skill in the art to distinguish between the presence or amount of atrial and brain natriuretic peptide prohormones that are present in the sample as a result of activation or inactivation of the hormonal system as recited in claim 1, and the presence or amount of atrial and brain natriuretic peptide prohormones that are present in the sample as a result of the presence of the fusion polypeptide. While the claim recites contacting steps, it fails to ***explicitly*** recite method steps directed to **detection** of the atrial and brain natriuretic peptide prohormones that are present in the sample and distinguishing said peptides from the added agent. Thus, performing the steps of the claimed method would not achieve the stated goal, which is determining activation or inactivation of the atrial natriuretic peptide and brain natriuretic peptide hormonal systems by detecting the presence or amount of proANP and proBNP in a sample from the subject.

Applicants assert that the rejection be withdrawn in light of amendment to the claims to recite "wherein said fusion polypeptide agent or said fusion peptide agent can be bound by a first binding substance, and said fusion polypeptide agent or said fusion peptide agent is used as a calibration agent or a competitive inhibitor" (Remarks of 6 April 2010, page 29, last paragraph). The amendment does not overcome the rejection. Absent any recitation that the fusion polypeptide or peptide is labeled in some way that would distinguish the calibration agent or competitive inhibitor from the proANP or proBNP that is present in the sample to be tested, one would not be able to distinguish between the presence or amount of atrial and brain natriuretic peptide prohormones that are present in the sample as a result of activation or inactivation of the hormonal system as recited in claim 1, and the presence or amount of atrial and brain natriuretic peptide prohormones that are present in the sample as a result of the presence of the fusion polypeptide.

The remainder of the claims is included in the rejection as dependent upon a rejected claim.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement

Claims 1-4, 7-17, 46, 47, 52, 59, 60, and 62-68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining activation of the ANP and BNP hormonal system and using said method to diagnose heart failure or monitor treatment of a cardiac condition, said method comprising detecting in a single reading, in a single assay the presence of atrial and brain natriuretic peptide prohormones or fragments thereof which comprises:

Contacting the sample with a bi-or oligospecific first binding substance wherein said binding substance is an antibody or antigen binding fragment thereof

said binding substance being able to bind to

a) (i) (i) proANP (SEQ ID NO:1), ANP (SEQ ID NO:2) or NT-proANP (SEQ ID NO:3), (the elected species)

b) (i) pro-BNP (SEQ ID NO:4), BNP (SEQ ID NO:5) or NT-proBNP (SEQ 1D NO:6) (the elected species) and

c) a fusion polypeptide comprising both (a) and (b)

wherein, compared to a reference level, detection of an increase in the presence of proANP and proBNP in the sample indicates activation of the ANP and BNP hormonal systems, and wherein compared to a reference level, detection of a decrease in the presence of proANP and proBNP in the sample indicates inactivation of these systems

thereby diagnosing heart failure if activation of the ANP and BNP hormonal systems is detected or thereby monitoring successful treatment of a cardiac condition if inactivation of ANP and BNP hormonal systems is detected

does not reasonably provide enablement for a method comprising

Contacting the sample with a bi-or oligospecific first binding substance wherein said binding substance is an antibody or antigen binding fragment thereof

said binding substance being able to bind to

a fragment of (a) or (b) which is at least 6 amino acids in length or

a naturally occurring species homologue or a naturally occurring allelic variant of (a) or (b)

This rejection is maintained for reasons of record and now applied to newly submitted claims 62-68.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988).

The claims are broadly drawn to a method comprising contacting the sample with a binding substance (antibody) that binds to both a sequence of SEQ ID NOs:1-3 and SEQ ID NOs:4-6 or naturally occurring species homologues or naturally occurring allelic variants or a fragment of SEQ ID NOs:1-3 and SEQ ID NOs:4-6 which is at least 6 amino acids in length and using the results obtained by said method to diagnose or monitor cardiac disease. One of ordinary skill in the art would be unable to practice this method utilizing a binding substance (antibody) to detect naturally occurring species homologues or naturally occurring alleleic variants of the recited sequences or a

fragment of SEQ ID NOs:1-3 and SEQ ID NOs:4-6 which is at least 6 amino acids in length. The full scope of the claims is not enabled for the following reasons.

The specification defines variant polypeptides as those "having the same essential character as or a basic biological functionality of the relevant polypeptide. ..... Typically a variant comprises an amino acid sequence which is homologous to all or a part of the sequence of the polypeptide. .....Variants may include allelic variants, species homologues and the deletion, modification or addition of single amino acids or groups of amino acids within the protein sequence, as long as the peptide maintains a basic biological functionality of the subject polypeptide" [paragraph 0108]. In one embodiment, the homologous variant and/or the fragment is at least 6 amino acids in length [paragraph 0178]. Thus, the polypeptide variants, as disclosed by the specification, encompass a myriad of polypeptides including polypeptides with deletions, modifications or additions of groups of amino acids within the protein sequence [paragraph 108], without the limitation of an upper limit to the number of deletions, modifications or additions and variants which may have no structural similarity to the referenced sequences. SEQ ID NO:3 is a polypeptide of 98 amino acid residues; SEQ ID NO:6 is a polypeptide of 76 amino acid residues. One of ordinary skill in the art could prepare the myriad of sequences having the recited deletions, modifications or additions of groups of amino acids within the protein sequence or prepare fragments of 6 amino acids in length and prepare a binding substance (such as an antibody) to each of the myriad of variants encompassed by the claims. However, applicants have not taught how to identify which of said variants would retain the structural and physiological characteristics of an ANP or a BNP such that one could correlate the changes in levels of such fragments and variants with the presence or absence of heart failure; one could not predict that detecting changes in the levels of any of the myriad of variants would be indicative of changes in activation of the atrial natriuretic peptide and brain natriuretic peptide hormonal systems and would be diagnostic of heart failure or useful in monitoring cardiovascular disease. Additionally, with regard to allelic variants or species homologues: while the specification discloses that said variants and homologues retain the biological functionality of the recited sequences, the specification

is silent as to the structural characteristics of said variants or homologues. Thus, one of ordinary skill in the art would be unable to predict that binding substances (antibodies) which bind to polypeptides of SEQ ID NO:3 and SEQ ID NO:6 would be able to bind to said variants and homologues.

As noted above, the claims recite detection of fragments of SEQ ID NO:3 and 6 at least 6 amino acids in length would be useful in the methods of the instant invention and could be used to diagnose heart failure or monitor the efficacy of treatment..

However, the art teaches that amino acid fragments that are 100% identical to at least 6 amino acid fragments of SEQ ID NOs: 3 or 6 are found in polypeptides that have no relationship to NT-pro-ANP or NT-proBNP polypeptides.

Flashner et al. (1996. Mol Microbiol. 19:985, cited in previous office action) teaches a sequence comprising a 7 amino acid fragment that is 100% identical to a 7 amino acid fragment of SEQ ID NO:3 (See results in SCORE and alignment below). The sequence is identified as a sequence present in *E. coli*

```
 Query Match          7.1%;  Score 7;  DB 2;  Length 181;
 Best Local Similarity  100.0%;  Pred. No. 24;
 Matches   7;  Conservative   0;  Mismatches   0;  Indels   0;  Gaps   0;

Qy          83 SALLKSK 89
               |||||||
Db          41 SALLKSK 47
```

Parkhill et al. (2001. Nature 413:848, cited in previous office action) teaches a sequence comprising a 7 amino acid fragment that is 100% identical to a 7 amino acid fragment of SEQ ID NO:3 (See results in SCORE and alignment below). The sequence is identified as a part of a polypeptide present in multiple drug resistant *Salmonella enterica*.

```
Query Match          7.1%;  Score 7;  DB 2;  Length 192;
 Best Local Similarity  100.0%;  Pred. No. 26;
 Matches   7;  Conservative   0;  Mismatches   0;  Indels   0;  Gaps   0;

Qy          48 ALSPLPE 54
               |||||||
Db          44 ALSPLPE 50
```

Parkhill et al (2000. Nature 403:665, cited in previous office action) teach a sequence comprising a 7 amino acid fragment that is 100% identical to a 7 amino acid fragment of SEQ ID NO:6 of the instant invention (See results in SCORE and alignment below). The sequence is identified as a part of a polypeptide present in the food-borne pathogen *Campylobacter jejuni*.

```
Query Match          9.2%;  Score 7;  DB 2;  Length 429;
 Best Local Similarity  100.0%;  Pred. No. 25;
 Matches   7;  Conservative   0;  Mismatches   0;  Indels   0;  Gaps   0;

Qy          33 VEQTSLE 39
               |||||||
Db         106 VEQTSLE 112
```

Solomon et al. (1992. Yeast 8:273, cited in previous office action) teach a sequence comprising a 7 amino acid fragment that is 100% identical to a 7 amino acid sequence of SEQ ID NO:6 of the instant invention (See results in SCORE and alignment below). The sequence is identified as a part of a polypeptide present in the yeast, *Saccharomyces cerevisiae*.

```
 Query Match          9.2%;  Score 7;  DB 2;  Length 571;
 Best Local Similarity  100.0%;  Pred. No. 32;
 Matches   7;  Conservative   0;  Mismatches   0;  Indels   0;  Gaps   0;

Qy           7 GSASDLE 13
               |||||||
Db         563 GSASDLE 569
```

Stover et al (2000. Nature 406:959, cited in previous office action) teach a sequence comprising a 7 amino acid fragment that is 100% identical to a 7 amino acid fragment of SEQ ID NO:6 of the instant invention (See results in SCORE and alignment below). The sequence is identified as part of a polypeptide of *Pseudomonas aeruginosa,* a major opportunistic pathogen.

```
 Query Match          9.2%;  Score 7;  DB 2;  Length 610;
 Best Local Similarity  100.0%;  Pred. No. 34;
 Matches   7;  Conservative   0;  Mismatches   0;  Indels   0;  Gaps   0;

Qy           6 PGSASDL 12
               |||||||
Db         254 PGSASDL 260
```

One of ordinary skill in the art would recognize that fragments of polypeptides of such common pathogens as *E. coli, Salmonella enterica, Campylobacter jejuni, Saccharomyces cerevisiae*, or *Pseudomonas aeruginosa* could be present in samples taken from subjects recited in the claims of the instant invention. However, applicants have provided no guidance as to how one of ordinary skill in the art would be able to distinguish from false positives generated by detection of such fragments and detection of unspecified and uncharacterized variants or fragments of at least 6 amino acids in length of NT-pro-ANP or NT-proBNP polypeptides; thus undue experimentation would be required to use the methods of the instant invention as a diagnostic method or to monitor the efficacy of treatment of cardiac disease as required by the claims of the instant invention.

It would require undue experimentation to prepare the myriad of sequences that meet the limitations recited in the claims, prepare antibodies that bind to said substances and detect said substances in a sample from a subject and determine if the results of detection of levels of variant polypeptides and/or fragments is diagnostic of heart failure or monitors the efficacy of treatment of a cardiac condition.

Applicants traverse the rejection (Remarks, 6 April 2010, page 31, bridging page 33, 1st paragraph). The reasons for the traversal are:

(1) Applicants assert that the claims have been amended to specify that the first binding substance binds to full length sequences of (i) proANP, ANP, or NT-proANP, and (ii) proBNP, BNP, or NT-proBNP. Thus, in addition to the possibility of binding to a fragment of one of each of these sets of proteins (the ANP and the BNP-related sequences), the binding substance also must bind to a full length ANP and BNP-related sequence. Similarly, the method claims have been amended to specify that the fusion polypeptide agent or fusion peptide agent binds to a binding substance that binds to a full length sequences noted above. A binding substance, such as an antibody, does not recognize an entire protein. Rather, it binds to and thus recognizes only a small part of the protein (i.e., an epitope). Because of this, it is reasonable to include fragments, in the claims, as that is what is actually being recognized in the context of the full length

sequence. This is not overly broad, as the only fragments that are covered are those that are recognizable in the context of the full length sequences as well, in view of the above-described amendment.

(2) The Examiner refers to teachings in the art of fragments having sequences that are 100% identical to at least 6 amino acid fragments of SEQ ID NOs:3 or 6, to support the position that Applicants have not provided guidance as to how those skilled in the art could determine false positives generated by detection of such fragments, and detection of ANP and BNP fragments. Applicants first note that the fragments of the present claims must be at least 12 amino acids in length, rather than 6, as considered by the Examiner in this analysis. In particular, and referring to claim 3 as an example, the specified fusion polypeptide agent or fusion peptide agent comprises a fragment of both an ANP-related sequence (part (a) of the claim) and a fragment of a BNP-related sequence (part (b) of the claim), wherein each fragment is at least 6 amino acids in length, resulting in a fusion polypeptide agent or a fusion peptide agent of at least 12 amino acids in length. Therefore, the information concerning sequences of only 6 amino acids in length is not relevant to the present claims. In addition, as noted above, the binding substances of the invention are required to bind full-length sequences, in addition to possibly binding fragments.

(3) Applicants have amended the claims to specify that such homologues and variants are naturally occurring. Applicants respectfully submit that undue experimentation would not be required to use such homologues and variants in the present methods. In particular, once it was decided to carry out the present method with a particular subject or group of subjects, the relevant sequences of the subject or group of subjects could be determined (if not already known) and used in the present methods.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

In response to (1) and (2): it is noted that the features upon which applicant relies:

(1) in addition to the possibility of binding to a fragment of one of each of these sets of proteins (the ANP and the BNP-related sequences), the binding substance also must bind to a full length ANP and BNP-related sequence and

(2) the fragments of the present claims must be at least 12 amino acids in length, rather than 6; in particular, and referring to claim 3 as an example, the specified fusion polypeptide agent or fusion peptide agent comprises a fragment of both an ANP-related sequence (part (a) of the claim) and a fragment of a BNP-related sequence (part (b) of the claim), wherein each fragment is at least 6 amino acids in length, resulting in a fusion polypeptide agent or a fusion peptide agent of at least 12 amino acids in length

are not recited in the rejected claim(s).

It is the Examiner's position that the claims are recited in the alternative. The binding substance is able to bind to

(a) (i) proANP (SEQ ID NO:I), ANP (SEQ ID NO:2), or NT-proANP (SEQ ID NO:3); ***or***

(a) (ii) a fragment of (a)(i) which is at least 6 amino acids in length;

(b) (i) proBNP (SEQ ID NO:4), BNP (SEQ ID NO:5), or NT-proBNP (SEQ ID NO:6); ***or***

(b) (ii) a fragment of (b)(i) which is at least 6 amino acids in length;

(e) said fusion polypeptide agent or said fusion peptide agent

(Emphasis added by the Examiner).

Nowhere in the claims is the requirement that the binding substance bind to both a fragment of one of each of these sets of proteins (the ANP and the BNP-related sequences), ***and*** to a full length ANP and BNP-related sequence recited. There is also no requirement that the binding substance bind to both the fusion polypeptide and the fragments wherein said fragments are at least 6 amino acid in length. Thus, Applicants arguments that the fragments must be at least 12 amino acids in length are not understood, and are not persuasive.

As previously discussed, the claims under consideration are directed to a **method** of utilizing a myriad of variant polypeptides in a method directed to determination of activation or inactivation of a hormonal system and utilizing said

determination to diagnose a disease or monitor the efficacy of treatment of a disease. While it may not be undue experimentation to construct the myriad variant sequences and fragments and generate substances which bind to said variants and fragments, one would be unable to predict whether detection of any one of these unspecified variants and/or fragments would be indicative of activation or inactivation of the hormonal system; one could not predict that the method detecting such unspecified variants or fragments would be diagnostic of heart failure or could be used to monitor the efficacy of treatment of a heart condition. Thus, testing all of the myriad of variants and fragments encompassed by the claims in the methods of the instant invention to determine the presence of which would be diagnostic of heart failure or useful in the monitoring of efficacy of treatment of a heart condition would constitute undue experimentation.

With respect to (3): Applicants have amended the claims to specify that such homologues and variants are naturally occurring. The disclosure teaches that such homologues and variants are polypeptides which has the same essential character as or a basic biological functionality of the relevant polypeptide [paragraph 0108]. There is no teaching in the specification of any structural relationship between the claimed variants and the referenced sequences. Thus, one of ordinary skill would not predict that a binding substance which would bind to the referenced sequences would also bind to the recited variants and would detection of such substances would provide information useful in diagnosing heart failure or monitoring the efficacy of a therapeutic regimen.

The rejection is thus maintained.

Written Description

Claims 1-4, 7-17, 46, 47, 52, 59, 60, and 62-68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is maintained for reasons of record, and is now applied to newly submitted claims 62-68. Applicant is directed to the Written Description Training Materials, Revision 1, March 25, 2008.

The claims are method claims, and are drawn to assays utilizing binding substances which bind to polypeptides of SEQ ID NOs:1-6 or fragments thereof of at least 6 amino acids in length, naturally occurring species homologues, and naturally occurring allelic variants of said sequences. Thus, these claims are drawn to methods utilizing several genera: polypeptides of SEQ ID NOs:1-6, naturally occurring species homologues, naturally occurring allelic variants of said sequences and fragments of at least 6 amino acids in length of said sequences.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

With regard to polypeptides of SEQ ID NOs:1-6 or naturally occurring variants thereof: the claims require that the variants retain the functional characteristics of binding to a binding substance. However, the specification does not teach any relationship between the structure of the polypeptides and the function, binding to a binding substance (ie an antibody). The specification discloses a method which detects only one subset of the claimed genus; the method is used to measure serum levels of NT-proANP (SEQ ID NO:3, the elected species) and serum levels of NT-proBNP,(SEQ ID NO:6, the elected species) (Example 3, paragraph 0318). Additionally, the claims are drawn to naturally occurring species homologues and naturally occurring allelic variants. The specification fails to describe any such naturally occurring homologues or naturally occurring allelic variants and does not disclose any structure physical and/or chemical characteristics of such naturally occurring allelic variants. There is no disclosed correlation between the unknown allelic variants and the disclosed species of SEQ ID NOs:1-6. While the specification teaches methods of obtaining allelic variants and species homologues [paragraph 0109], possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features (see, Univ. of Rochester v. G.D. Searle & Co., 358 F.3d916, 927,69 USPQ2d 1886, 1895 (Fed. Cir. 2004); accord Ex Parte Kubin, 2007-0819, BPAI 31 May 2007, opinion at p. 16, paragraph 1).

The only methods taught are those utilizing the claimed genera of peptides of SEQ ID NOs:1-6 or variants thereof are methods utilizing pro-ANP (SEQ ID NO:1), ANP (SEQ ID NO:2), NT-proANP (SEQ ID NO:3, the elected species), proBNP (SEQ ID NO:4), BNP (SEQ ID NO:5) and NT-proBNP (SEQ ID NO:6, the elected species). However, the present claims encompass utilizing almost an infinite number of species that are not further described in the methods of the instant invention.

Therefore, only methods detecting polypeptides of SEQ ID NOs:1-6, but not the full breadth of the claims meet the written description provision of 35 U.S.C. 112, first paragraph.

Claims 18, 21, and 49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim (s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a fusion polypeptide agent of SEQ ID NOs:13-20 or fusion polypeptides comprising both one of (1a) SEQ ID NOs 1-3, or (1b) a fragment of one of (1a) which is at least 6 amino acids in length or (1c) a naturally occurring species homologue or a naturally occurring allelic variant of 1a

and

one of (2a) SEQ ID NOs 4-6, or (2b) a fragment of one of 2a which is at least 6 amino acids in length or (2c) a naturally occurring species homologue or a naturally occurring allelic variant of 2a

Thus, the claims are drawn to a myriad of fusion polypeptides which may comprise any of the polypeptides listed in 1a-c fused to any of polypeptides listed in 2 a-c, each component of the fusion polypeptide may comprise an almost infinite number of variants and/or fragments.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to a genus, i.e., fusion polypeptides of SEQ ID NOs:13-20 or fusion polypeptides comprising 1a-c and 2a-c in any combination, as described in the previous paragraph.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product or any combination thereof. The claims do not require that the fusion polypeptide possess any particular biological activity; the polypeptides are

identified only by a partial structure, that is a polypeptide comprising a fragment of SEQ ID NOs 1-3 and a fragment of SEQ ID NOs 4-6, said fragment being at least 6 amino acids in length, or fusion polypeptides comprising a naturally occurring species homologue or a naturally occurring allelic variant of 1a or 2a or any combination of said polypeptides, fragments, homologues or variants thereof.

There is not any identification of any particular portion of the referenced (SEQ ID NOs:1-6) polypeptide structures that must be conserved. As discussed above, the specification fails to describe any such naturally occurring homologues or naturally occurring allelic variants and does not disclose any structure physical and/or chemical characteristics of such naturally occurring allelic variants. There is no disclosed correlation between the unknown allelic variants and the disclosed species of SEQ ID NOs:1-6. While the specification teaches methods of obtaining allelic variants and species homologues [paragraph 0109], possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features (see, Univ. of Rochester v. G.D. Searle & Co., 358 F.3d916, 927,69 USPQ2d 1886, 1895 (Fed. Cir. 2004); accord Ex Parte Kubin, 2007-0819, BPAI 31 May 2007, opinion at p. 16, paragraph 1).

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide written description of the claimed genus.

There are 7 species of the claimed genus disclosed that is within the scope of the claimed genus, *i.e.* SEQ ID NOs 13-20. The disclosure of several disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claims encompasses a myriad of highly variant species comprising variant polypeptides and fragments of said polypeptides that are not further described.

Therefore, only fusion polypeptides comprising the amino acid sequences set forth in SEQ ID NOs:13-20, but not the full breadth of the claims meet the written description provision of 35 U.S.C. 112, first paragraph.

Claims 23-26 and 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim (s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polynucleotides comprising both (1a) SEQ ID NOs:7, 8 or 9 or (1b) a sequence complementary to any of sequences disclosed in (1a), or (1c) a sequence which is degenerate as a result of the genetic code to sequences disclosed in (1a-1b), or (1d) a fragment of any of sequences disclosed in 1a-1c wherein said fragment encodes a peptide of at least six amino acids in length or (1e) a naturally occurring species homologue or naturally occurring allelic variant of 1(a) or fragment of (1e) wherein said fragment encodes a peptide of at least six amino acids in length

and

(2a) SEQ ID NOs 10, 11, or 12 or (2b) a sequence complementary to any of sequences disclosed in (2a), or (2c) a sequence which is degenerate as a result of the genetic code to sequences disclosed in (2a-2b), or (2d) a fragment of any of sequences disclosed in 2a-2c wherein said fragment encodes a peptide of at least six amino acids in length or (2e) a naturally occurring species homologue or naturally occurring allelic variant of 2(a) or fragment of (2e) wherein said fragment encodes a peptide of at least six amino acids in length

The claims are drawn to an almost unlimited number of variant polynucleotides as they recite any combination of the 6 polynucleotides or variants thereof as described in 1a-1e and the 6 polynucleotides or variants thereof as described in 2a-2e.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claims indicate that these claims are drawn to a number of genera, i.e., nucleic acids encoding fusion polypeptides, said nucleic acids comprising sequences of

SEQ ID NOs 7, 8, or 9 and SEQ ID NOs 10, 11 or 12 or variants or homologues or fragments thereof as described in the previous paragraph.

The claims do not require that the nucleic acids encode polypeptides of any particular biological function. Thus, the claims are drawn to genera of nucleic acids that are defined only by sequence identity.

To provide evidence of possession of the claimed genera, the specification must provide sufficient distinguishing identifying characteristics of the genera. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product or any combination thereof. In this case, the only factor present in the claims is a partial structure in the form of a fragments or allelic variants. As discussed above, the specification fails to describe any naturally occurring homologues or naturally occurring allelic variants and does not disclose any structure physical and/or chemical characteristics of such naturally occurring allelic variants. There is no disclosed correlation between the unknown allelic variants and the disclosed species of SEQ ID NOs:1-6 and therefore there is no disclosed correlation between sequences encoding allelic variants and the disclosed sequences of SEQ ID NOs:7-12. While the specification teaches methods of obtaining allelic variants and species homologues, and thus the polynucleotides encoding said variants [paragraph 0109], possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features (see, Univ. of Rochester v. G.D. Searle & Co., 358 F.3d916, 927,69 USPQ2d 1886, 1895 (Fed. Cir. 2004); accord Ex Parte Kubin, 2007-0819, BPAI 31 May 2007, opinion at p. 16, paragraph 1).

Thus one would not conclude that the applicants are in possession of the claimed genus of nucleic acids.

Therefore only polynucleotides comprising : (1) (a) SEQ ID NOs:7, 8 or 9, (b) sequences complementary to SEQ ID NOs:7, 8 or 9 or sequences which are degenerate as a result of the genetic code to 1 a or b; and (2) (c) SEQ ID NOs: 10, 11 or 12 or (d) sequences complementary to SEQ ID NOs:10, 11 or 12 or sequences which

are degenerate as a result of the genetic code to 2 c or d, but not the full breadth of the claims meet the written description provision of 35 U.S.C. 112, first paragraph.

Claims 27 and 51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods of producing a fusion polypeptide agent comprising both one of (1a) SEQ ID NOs 1-3, or (1b) a fragment of one of (a) which is at least 6 amino acids in length or 1(c) a naturally occurring species homologue or a naturally occurring allelic variant of 1(a) or a fragment of said homologue or variant which is at least 6 amino acids in length

and

one of (2a) SEQ ID NOs 4-6, or (2b) a fragment of one of (2a) which is at least 6 amino acids in length or 2(c) a naturally occurring species homologue or a naturally occurring allelic variant of 2(a) or a fragment of said homologue or variant which is at least 6 amino acids in length

Thus, the claims are drawn methods of producing a myriad of fusion polypeptides which may comprise any of the polypeptides listed in 1a-c fused to any of polypeptides listed in 2a-c, each component of the fusion polypeptide may comprise an almost infinite number of variants and/or fragments.

Since the full breadth of the claims to the fusion polypeptides lack written description, for reasons discussed above, the full breadth of the claims directed to methods of making said fusion polypeptides also lack written description.

Therefore, only methods of making fusion polypeptides comprising the amino acid sequences set forth in SEQ ID NOs:13-20, but not the full breadth of the claims meet the written description provision of 35 U.S.C. 112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 115).

Applicants traverse the rejection (Response of 6 April 2010, page 6, last paragraph, bridging page 7, 1st paragraph). The reasons for the traversal are:

The claimed invention relates to new methods and reagents that can be used to carry out the methods, which reagents can be made based on known or readily identifiable sequences. In view of this those of skill in the art would consider that the present inventors were in possession of the invention to the extent of the full scope of the claims.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

Applicants' claims are drawn to a multitude of sequences. While these sequences are claimed in relationship to a referenced sequence, Applicants have not disclosed which amino acid residues must be retained for the required function, binding to a binding substance which is crucial to practicing the claimed method. Applicants claim fragments comprising as few as 6 amino acid residues which are identical to the referenced sequences. Applicants have described fragments of ANP and BNP [paragraph 0181]; however one cannot determine if these fragments are representative of the huge, highly variant genus recited in the claims of the instant invention. Applicants have disclosed that one may generate binding substances to the conserved ring structure of ANP and BNP; however, applicants' claims encompass variants and fragments which do not comprise these amino acid fragments. The art teaches these conserved regions would be found, for example, in proANP, the pro-peptide of 126 amino acid residues, and in ANP, the mature atrial natriuretic peptide formed by amino acids 99-126 of the prohormone, but would not be found in NT-proANP, the N-terminal fragment that is cleaved off during processing of the molecule (See, for example, Veale et al. 2000. Bioorganic and Medicinal Chem Let. 10:1949-1952, Figure 1, cited in previous office action). Thus, the claims encompass a myriad of highly variant structures; applicants have not disclosed sufficient information about structure/function relationships to enable one of ordinary skill to determine that applicants were in possession of the breadth of the polypeptides encompassed by the claims.

Since the full breadth of the claims to the fusion polypeptides lack written description, for reasons discussed above, the full breadth of the claims to polynucleotides encoding said fusion polypeptides also lack written description as do methods of producing said polypeptides.

35 U.S.C. § 103:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of Claims 1, 16, and 17 under 35 U.S.C. 103(a) as being unpatentable over Clerico et al (1998. J Endoc. Invest 21:170-179), in view of Clerico et al. (2000. Clin. Chemistry 46:1529-1534) is maintained and applied to newly presented claims 62-66 and 68 for reasons of record and for reasons set forth below.

It is noted that Claim 1, one of the independent claims of the instant invention has been amended to recite "wherein said method does not comprise detection of the presence of proANP and proBNP or fragments thereof individually". It is the Examiner's position that this amendment to the claim reinforces the preamble to the claim and does not remove the ideas that flow naturally from the teachings of the prior art, that the detection of proANP and proBNP may be performed in a single assay in a single reading.

The claims are drawn to an *in vitro* method comprising simultaneously detecting, in a single reading, in a single assay, the presence of atrial and brain natriuretic prohormones (proANP and proBNP) in a sample, wherein the method comprises an immunoassay (Claim 16), thereby diagnosing heart failure or monitoring treatment of a cardiac condition (Claim 17). Newly presented claims are directed to a method wherein said reference level is determined from a previous measurement from said subject (Claim 62), wherein said reference level is based on the normal level of a population of subjects (Claim 63), wherein said population of subjects is the general population (Claim 64), wherein said assay is calibrated so that a particular reading in the assay is known to represent the normal peptide level (Claim 65), wherein said assay is calibrated so that a normal level will produce a negligible or insignificant result (Claim 66) wherein said subject is a human (Claim 68).

Clerico et al (1998) teach measurement of plasma atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels in plasma of patients with heart failure as an assay method useful in follow-up of cardiac patients (monitoring a cardiac condition) (abstract). The measurements are performed on plasma samples from healthy human subjects and patients with chronic cardiomyopathy (page 172, 1st column, 2nd paragraph). The measurements from healthy, normal subjects in the general population were used to establish a reference level of normal ANP and normal BNP levels (Figure

3). Both polypeptides were measured in samples from the same subject (page 174, 1st column, 3rd paragraph and page 175, 2nd column, last paragraph); absent evidence to the contrary, said measurements would constitute simultaneous detection. The measurements were performed using non-competitive immunoradiometric assays (IRMA) (page 172, 1st column, last paragraph bridging page 173, 2nd column, 1st paragraph). The reference teaches utilizing standard solutions comprising known quantities of ANP and BNP to generate standard curves which act as reference values to determine the amount of ANP and BNP in the samples from patient subject (Page 172, 2nd column, 2nd paragraph and page 173, 1st column, 1st paragraph). While the reference does not teach determining a reference level from a previous measurement from the same subject, the reference does teach that the assay methods for these peptides may be useful in the follow-up of cardiac patients, thus teaching the advantage of comparing the detected level of the natriuretic peptides in one assay to those detected in a sample from the same patient in a previously performed assay.

Clerico et al (1998) does not teach a method comprising detecting the presence of atrial and brain natriuretic peptide prohormones or fragments thereof. Clerico et al (2000) teach that cardiac natriuretic hormones are a family of related peptides including ANP, BNP and other peptides derived from the N-terminal portion of proANP and proBNP peptide chains (abstract). The reference teaches that the N-terminal prohormones (NT-proANP and NT-proBNP) are present in greater amounts in the plasma than ANP and BNP (Table 1).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the methods taught by Clerico et al (1998) and substitute measurement of proANP and proBNP (as taught by Clerico et al (2000)) for the measurement of ANP and BNP as taught by Clerico et al. (1998). The person of ordinary skill in the art would have been motivated to make these modifications because Clerico et al (2000) teach that the prohormones are present in higher concentrations in the plasma and one of ordinary skill in the art would recognize that these may be measured more easily and accurately. One would reasonably have expected success because methods of measuring said prohormones are outlined by Clerico et al (2000).

Additionally, one of ordinary skill, aware that it is routine to detect multiple compounds in a single sample at the same time in the performance of clinical assays (for example, a lipid profile, liver enzyme assays), would be motivated to assay both ANP and BNP in the same assay to increase the efficiency and reduce the costs of said assays. Techniques utilizing immunoassays for simultaneous detection of two polypeptides in a single reading in a single assay were well known at the time of the instant invention, as evidenced by Swartzman et al which teaches simultaneous detection of two cytokines, IL-6 and IL-8 in the same high-throughput multiplexed immunoassay. (See, for evidentiary purposes only, Swartzman et al. 1999. Analytical Biochem. 271:143-151, abstract)

Absent evidence that assaying for one protein, i.e. detection of ANP, would interfere with the detection of the second protein, i.e. detection of BNP, one of ordinary skill would anticipate success in detecting both proteins simultaneously in the same sample.

With respect to the limitations recited in Claims 65 and 66. While the references do not teach assays calibrated so that a particular reading in the assay is know to represent the normal peptide level (Claim 65) or assays wherein the assay is calibrated so that a normal level will produce a negligible or insignificant result (Claim 66), one of ordinary skill in the art is aware that calibration of read-out instruments, such as FACs machines or counters which detect radioactivity, to set base-line levels at pre-determined, desired levels is routine in the art of immunoassays.

Applicants traverse the rejection (Response of 8 April 2010, page 33, 3rd paragraph, bridging page 35, 1st paragraph). The reasons for the traversal are:

1. Claim 1 requires a single reading, in a single assay of the presence of proANP and proBNP, or fragments thereof. Rather, the references require at least two readings to obtain information with respect to both ANP and BNP-related sequences.

2. Nowhere does either Clerico (1998) or Clerico (2000) teach or suggest the measurement of the presence of proANP and proBNP in a single reading, in a single assay. When considered as a whole, Clerico (1998) provides a rationale for measuring ANP and BNP separately as "the data reported in Figure 3 suggest that the BNP assay

is more useful than the ANP assay for discriminating between normal subjects and patients with cardiomyopathy, even including those with only mild symptoms" (page 176, column 1). Furthermore, Clerico (2000) states:

[A]lthough ANP and BNP bind to the same specific receptors, they have different types of metabolism and spectra of biological activity, and their production and secretion may be regulated differently in humans. It has been suggested that there may be different pools of intracellular natriuretic peptides that can respond separately to the same hemodynamic events (e.g., overload for ANP) or to the same pathology-related factors (e.g., cardiac hypertrophy for BNP). (Page 1530, column 1). Based on these statements, Clerico (1998) and Clerico (2000) teach the desirability of distinguishing between ANP and BNP levels and, therefore, teach away from the claimed methods, which require a single reading, in a single assay, showing the presence of proANP and proBNP, without distinguishing between the two polypeptides.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

In response to 1: While the Cicero references do not teach detection of both natriuretic peptides without the detection of the presence of proANP or proBNP individually, as the amended claim now recites, this amendment to the claim reinforces the preamble to the claim and does not remove the ideas that flow naturally from the teachings of the prior art, that the detection of proANP and proBNP may be performed in a single assay in a single reading. One of ordinary skill, aware of the teachings of the cited references, and in the interests of efficiency could easily design such an assay: for example by labeling an antibody to pro-ANP and an antibody to pro-BNP (a mixture of mono-specific binding substances) with the same detectable label. By doing so, one would detect both proteins in the same reading. Absent evidence that assaying for one protein, i.e. detection of ANP, would interfere with the detection of the second protein, i.e. detection of BNP, one of ordinary skill would anticipate success in detecting both proteins simultaneously in the same sample.

In response to 2: The data presented in Figure 3 of Clerico et al (1998) clearly demonstrates that **both** ANP and BNP levels are significantly increased in cardiac patients. The reference teaches "As a whole, cardiac patients showed ANP levels significantly ...higher than those observed in normal subjects. However, because

circulating ANP levels tended to increase with the progression of clinical severity of the disease, some patients with only mild ventricular dysfunction can show ANP levels within the normal range ....while patients with more severe heart failure generally show greatly increased values". (page 174, 1st column, 4th paragraph, emphasis added by Examiner). "Circulating BNP levels increased with the progression of clinical severity of disease, consequently patients with more severe disease showed greatly increased values compared to patients with mild symptoms of disease" (page 174, 2nd column). It is noted that the levels of ANP measured in cardiac patients are never lower than those in normal patients. Thus, while differences in BNP levels may be a better diagnostic indicator of *mild* cardiovascular disease, the reference teaches that both ANP and BNP are greatly elevated in patients with clinical severe disease, such as severe heart failure. One of ordinary skill would conclude that elevated levels of BNP, ANP or both would be diagnostic of heart failure, as recited in claim 17 of the instant invention.

Clerico et al (2000) discusses the possibility of different pools of intracellular natruiretic peptides; but it is unclear how this is relevant to the issue at hand, which is whether the references teach away from the fact that increases in levels of ANP and BNP are found in patients with heart failure, and thus would be diagnostic of heart failure. The reference nowhere teaches that measurement of ANP, BNP or both would not result in useful clinical information. Clerico et al. (2000) teach "Several recent studies have underlined the clinical importance to routinely assay CNHs (cardiac natriuretic hormones, including ANP and BNP) for classification, follow-up, and/or prediction of mortality/survival rates of all patients with heart failure" (Page 1533, 1st column, 1st paragraph). "In some studies, the assay for N-terminal proANP1-98 peptides (the elected species of the instant invention) was shown to be equally or even more clinically useful than other CNH assays, whereas in others BNP was found to be the best marker of myocardial involvement." (page 1532, 1st column, 1st paragraph). Thus, taken as a whole, the two references establish that both ANP and BNP levels are elevated in patients with severe heart failure and measuring either or both would provide important clinical information.

The rejection is thus maintained.

The rejection of Claims 2-4, 7-15, 46, 47, 59 and 60 under 35 U.S.C. 103(a) as being unpatentable over Clerico et al (1998) in view of Clerico et al. (2000) as applied to claim 1 further in view of Buechler et al (US 7,341,838, filed 19 April 2004, priority claimed to provisional application 60/466,358, filed 28 April 2003, the '838 patent) is maintained and applied to newly presented claim 67 for reasons of record and for reasons set forth below.

The teachings of Clerico et al (1998) and Clerico et al (2000) are outlined in detail above. In addition to the teachings above, Clerico et al. (2000) teach competitive assays such as radioimmunoasssays comprising labeled antigens such as ANP and BNP (abstract).

The references, singly or in combination, do not teach the following further limitations:

contacting the sample with a bi- or oligo-specific binding substance that is able to bind to both NT-proANP of SEQ ID NO:3 and NT-proBNP of SEQ ID NO:6 and a fusion polypeptide (Claims 2, 3, 46 and 59),

wherein said fusion polypeptide agent is used as a calibration agent or competitive inhibitor (claims 3 and 67)

wherein the fusion polypeptide comprises pro-BNP1-76 (SEQ ID NO:6) and proANP 1-98 (SEQ ID NO:3) (claims 9-11),

wherein the binding substance comprises a bi- or oligo specific binding substace or a mixture of mono-specific binding substances (Claim 4), an antibody that binds to NT-proANP of SEQ ID NO:3 and NT-proBNP (SEQ ID NO:6) (Claims 7 and 8), wherein the first binding substance or agent is labeled and/or immobilized (claim 12) and a method which additionally comprises contacting the sample with a second binding substance which is able to bind to the first binding substance, wherein the second binding substance is labeled or immobilized and wherein a precipitate is formed (claims 13-15)

a method of claim 1 which comprises contacting the sample with a fusion polypeptide comprising both SEQ ID NO:3 and SEQ ID NO:6 and a first binding

substance which is able to bind to SEQ ID NO:3 and SEQ ID NO:6 and said fusion polypeptide (Claim 47)

wherein the first binding sequence binds to both SEQ ID NO:3 or fragments thereof which are at least 6 amino acids in length SEQ ID NO:6 or fragments thereof which are at least 6 amino acids in length (Claim 52)

It is noted that the claims include the presence of a fusion polypeptide comprising both pro-ANP and pro-BNP (for example, Claims 2, 3, 9-11, 46, 47 and 59). The claims, as discussed above, are vague and indefinite in that they do not clearly indicate how one of ordinary skill would be able to distinguish the atrial and brain natriuretic peptide prohormones that may be present in the sample (which are to be detected) in unknown quantities from the added fusion polypeptide which comprises pro-ANP and pro-BNP. The Examiner has interpreted these claims to be directed to a non-competitive or a competitive binding assay, such as a radioimmunoassay.

The references do not teach the utilization of a fusion polypeptide as a standard or a competitive antigen. However, as discussed above, Clerico et al. (1998) teach using standards of ANP and BNP in the assays for these natriuretic hormones and also teach radioactively labeled antibodies to said peptides (Figures 1 and 2); Clerico et al (2000) teach competitive radioimmunoassays (abstract) and teach the advantages of measuring the prohormones (pro-NT-ANP and pro-NT-BNP). Since, as discussed above, it would be obvious to measure both pro-ANP and pro-BNP in the same assay to increase the efficiency and reduce the costs of said assays, it would be obvious to one of skill in the art to make a fusion protein so that one could have a protein comprising equimolar amounts of pro-BNP and pro-ANP to use as a standard in immunoassays detecting both polypeptides in a single assay. One would have a reasonable expectation of success because methods of making fusion protein are well known in the art.

The '838 patent teaches methods of determining treatment regimen for use in a patient comprising determining the presence of fragments of ANP, BNP and CNP

precursor peptides or fragments thereof utilizing immunoassays and correlating the presence or amount of said fragments of ANP and BNP to a disease or prognostic state (column 10, lines 53-67)

The '838 patent also teaches a sequence (SEQ ID NO:3) comprising a segment, amino acids 1-98, which is 99.4% identical to SEQ ID NO:3 of the instant invention and is identified as an ANP precursor, pro-ANP (identified as proANP 1-98 of claim 10) (pro-hormone) (See results in SCORE and alignment below).

Alignment match for SEQ ID NO:3 of the instant invention

```
  Query Match             99.4%;  Score 509;  DB 3;  Length 126;
  Best Local Similarity   99.0%;  Pred. No. 4.6e-52;
  Matches   97;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 NPMYNAVSNADLMDFKNLLDHLEEKMPLEDEVVPPQVLSEPNEEAGAALSPLPEVPPWTG 60
              ||||||||||||||||||||||||||||||||||||||||:||||||||||||||||||||
Db          1 NPMYNAVSNADLMDFKNLLDHLEEKMPLEDEVVPPQVLSDPNEEAGAALSPLPEVPPWTG 60

Qy         61 EVSPAQRDGGALGRGPWDSSDRSALLKSKLRALLTAPR 98
              ||||||||||||||||||||||||||||||||||||||
Db         61 EVSPAQRDGGALGRGPWDSSDRSALLKSKLRALLTAPR 98
```

It is noted that the one amino acid difference between the sequence as taught by the '838 patent and the instant invention is a conservative amino acid substitution of Aspartic acid for Glutamic acid; one of ordinary skill would predict that this conservative substitution would not effect the biological activity, binding characteristics, or three-dimensional configuration of the protein.

The reference also teaches a sequence, SEQ ID NO:1, comprising a segment, amino acids 1-76 which is 100% identical to SEQ ID NO:6 of the instant invention and is identified as a BNP-precursor molecule (proBNP 1-76 of claim 10) (pro-hormone) (See results in SCORE and alignment below).

Alignment match for SEQ ID NO:6 of the instant invention

```
  Query Match             100.0%;  Score 392;  DB 3;  Length 108;
  Best Local Similarity   100.0%;  Pred. No. 4.1e-41;
  Matches   76;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;
```

```
Qy          1 HPLGSPGSASDLETSGLQEQRNHLQGKLSELQVEQTSLEPLQESPRPTGVWKSREVATEG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 HPLGSPGSASDLETSGLQEQRNHLQGKLSELQVEQTSLEPLQESPRPTGVWKSREVATEG 60

Qy         61 IRGHRKMVLYTLRAPR 76
              ||||||||||||||||
Db         61 IRGHRKMVLYTLRAPR 76
```

One of ordinary skill in the art would recognize that binding substances or antibodies which recognize polypeptides comprising segments 99.4% and 100% identical to SEQ ID NO:3 and SEQ ID NO:6, respectively, of the instant invention would recognize the polypeptides of the instant invention. The '838 patent teaches measuring fragments in samples; said fragments could be pro-ANP and pro-BNP (column 15, lines 36-43). The fragments are recognized by antibodies. Said antibodies may comprise bivalent antibodies, comprising two Fab fragments linked by a disulfide bridge at the hinge region (column 16, lines 21-23), thus teaching a bispecific binding substance that binds to proANP and proBNP, as required by claims 2, 3, 7, 46, 47, and 59). The antibodies may be monoclonal antibodies or polyclonal antibodies (column 16, lines 34-39), as required by claim 8. The reference teaches immunoassays comprising a tagged antibody (column 18, lines 24-26), a limitation of claim 12. The reference teaches a pure preparation of the known antigen (pro-ANP and pro-BNP, in the instant assay) is needed in order to standardize the assay (column 18, lines 35-40). The '838 patent teaches immunoassays comprising labeled anti-immunoglobulin antibodies (column 18 lines 53-55), thus meeting the limitations of claims 13 and 14. The reference also teaches "capture" or "sandwich" ELISA assays wherein the antigen-antibody-2nd antibody complex precipitates (column 18, line 60, bridging column 19, line 3) and radioimmunassays (column 18, lines 32-55).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the methods taught by Clerico et al (1998) and Clerico et al (2000) and substitute the polypeptides of SEQ ID NOs: 3 and 1 as taught by the '838 patent for the generic proANP and pro-BNP taught by the Clerico et al (2000) and utilize the antibodies and immunoassays taught by the '838 patent in place of the IRMA assays taught by Clerico et al (1998). The person of ordinary skill in the art

would have been motivated to make these modifications because the '838 patent identifies the polypeptides of SEQ ID NOs:3 and 1 as proANP and pro-BNP and one of skill in the art would recognize that one may use bivalent antibodies to bind to different antigens, antibodies directed to the full length sequence would also bind homologous sequences or fragments of said sequences and that different types of immunoassays (RIAs, IRMAs and ELISAs) are art-recognized equivalents. Additionally, as discussed above, one would be motivated to make a fusion polypeptide, as recited in claim 10(d) comprising SEQ ID NOs:3 (proBNP 1-76) and SEQ ID NO:1 (proANP 1-98), sequences taught in the '838 patent, to use as a standard in the assays to detect both pro-ANP and pro-BNP in a single assay so that one could have a protein comprising equimolar amounts of pro-BNP and pro-ANP to use as a standard in immunoassays using bivalent antibodies. One would reasonably have expected success because the references listed above teach utilizing standards comprising ANP and BNP in the immunoassays, and methods of making fusion proteins and bivalent antibodies for use in diverse immunoassays and methods of practicing different immunoassays are well known in the art. Additionally, although the polypeptide of the prior art (SEQ ID NO:3) differs by one conservative amino acid substitution from the sequence of the claimed invention, one of ordinary skill would recognize, absent evidence to the contrary, that polypeptides comprising said sequence would have the same structural and biological characteristics (for example, binding, and antigenicity) as the polypeptide of the instant invention.

Applicants traverse the rejection (Response of 6 April 2010, page 35, 4th paragraph, bridging page 36, 1st paragraph). The reasons for the traversal are:

A central feature of the claimed invention is the detection of the presence of both proANP and proBNP-related sequences in a single reading, in a single assay. Also as discussed above, it would not have been obvious in view of either Clerico reference to perform a single assay to obtain a single reading that determines the presence of proANP and proBNP, without distinguishing between the two polypeptides. Buechler ('838) does not add what is missing from the Clerico references in supporting this rejection, as Buechler ('838) does not teach or suggest testing for the presence of proANP and proBNP-related sequences in a single reading, in a single assay.

Applicant's arguments have been fully considered but are not found to be persuasive.

The reasons for maintenance of the rejection of Claim 1 over both Clerico references are set forth in detail above.

One of ordinary skill in the art, aware that it is routine to detect multiple compounds in a single sample at the same time in the performance of clinical assays, would be motivated to assay both ANP and BNP in the same assay to increase the efficiency and reduce the costs of said assays. Absent evidence that assaying for one protein, i.e. detection of ANP, would interfere with the detection of the second protein, i.e. detection of BNP, one of ordinary skill would anticipate success in detecting both proteins simultaneously in the same sample. The '838 patent is cited for teaching specific sequences of pro-ANP and pro-BNP identical to those recited in the claims of the instant invention and reciting details of immunoassays using bispecific antibodies and providing details not taught by the Clerico references.

The rejection is thus maintained.

The rejection of Claims 18-21, 27, 49, and 51 under 35 U.S.C. 103(a) as being unpatentable over Burnett et al (US 6,818,619, filed 26 March 2002, the '619 patent) in view of Buechler et al (the '838 patent) is maintained for reasons of record and for reasons set forth below.

The claims are drawn to a fusion polypeptide comprising ANP and BNP or variants thereof and methods of making such polypeptides recombinantly.

The '619 patent teaches natriuretic peptides (NP) which include ANP, CNP, BNP or DNP, portions of a NP, variants of a NP or chimeras thereof (column 5, lines 27-29). The reference specifically describes a chimeric polypeptide comprising BNP with DNP (column 2, line 66, bridging column 3, line 1). The reference also teaches a chimeric protein, VNP, which comprises ANP and CNP (column 2, lines 16-19). Thus, the reference provides generic teachings of chimeric proteins comprising natriuretic peptides or variants thereof. The '619 patent teaches that said chimeric peptides have

combined effects in vivo, which includes vasodilation, natriuresis and suppression of rennin (column 3, lines 59-61), and thus would be valuable as therapeutic polypeptides. The reference teaches said chimeric proteins may be prepared by using recombinant DNA based technology (column 10, lines 37-39). Recombinant DNA can be readily introduced into the host cell so that the DNA molecules are expressed by the host cell (column 13, lines 46-55) and the protein thus produced.

While the '619 patent does not teach a chimeric protein specifically comprising ANP and BNP, the reference does teach specific chimeric proteins comprising each individual protein fused to second natriuretic polypeptide. Additionally, the reference teaches chimeric peptides comprising any of four identified natriuretic polypeptides, thus presenting generic teachings of fusion proteins comprising natriuretic polypeptides. Thus, it would be obvious to the person of ordinary skill in the art at the time the invention was made to modify the specific fusion proteins taught by the '619 patent which comprise BNP and DNP or ANP and CNP and construct a fusion protein comprising ANP and BNP. One of ordinary skill in the art would be motivated to make such a fusion protein and would anticipate success because the '619 patent teaches chimeric natriuretic peptides may comprise ANP, CNP, BNP or DNP, portions of a NP, or variants of a NP and teaches the therapeutic advantages of such chimeric polypeptides; furthermore, methods of making fusion proteins are well known in the art, and are taught by the '619 patent.

Additionally, under KSR, it is now apparent "obvious to try" may be an appropriate test in many situations. Where there is motivation to solve a problem, in the instant case, producing a therapeutic polypeptide with combined effects of two natriuretic polypeptides and there are a finite number of identified, predictable solutions, in the instant case, a maximum of 12 possible polypeptides, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation, but of ordinary skill and common sense. The fact that a combination was obvious to try might show that it

was obvious under 103. (KSR Int'lCo. V. Teleflex Inc,. 127 S. Ct. 1727. 82 USPQ2d 1385, 1397 (2007)).

The '619 patent does not teach a fusion polypeptide agent comprising any of the components as recited in claims 18-20. Specifically, the '619 patent does not teach a fusion polypeptide agent comprising a fusion polypeptide agent comprising proBNP1-108 and proANP1-126 (Claim 19(f)) which comprises SEQ ID NO:19 (Claim 20).

The '838 patent teaches polypeptides which comprise sequences comprising segments that are 99.4% and 100% identical to SEQ ID NO:3 and SEQ ID NO:6, respectively (See alignment above). The '838 patent also teaches sequences comprising proBNP1-108 (SEQ ID NO:1 disclosed in the '838 patent) and a proANP1-126 (SEQ ID NO:3 disclosed in the '838 patent) (See results in SCORE); said polypeptides are recited as components of the fusion polypeptide recited in claim 19(f); the recited components comprise SEQ ID NO:19 as recited in claim 20 (See alignments below).

Alignment match for amino acids 1-108 of SEQ ID NO:19 of the instant invention (Claims 19f and 20)

```
  Query Match             45.9%;  Score 561;  DB 3;  Length 108;
  Best Local Similarity   100.0%;  Pred. No. 3.6e-49;
  Matches  108;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 HPLGSPGSASDLETSGLQEQRNHLQGKLSELQVEQTSLEPLQESPRPTGVWKSREVATEG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 HPLGSPGSASDLETSGLQEQRNHLQGKLSELQVEQTSLEPLQESPRPTGVWKSREVATEG 60

Qy         61 IRGHRKMVLYTLRAPRSPKMVQGSGCFGRKMDRISSSSGLGCKVLRRH 108
              ||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 IRGHRKMVLYTLRAPRSPKMVQGSGCFGRKMDRISSSSGLGCKVLRRH 108
```

Alignment match for amino acids 109-234 of SEQ ID NO:19 of the instant invention (Claims 19f and 20).

```
  Query Match             53.9%;  Score 659;  DB 3;  Length 126;
  Best Local Similarity   99.2%;  Pred. No. 4.6e-59;
  Matches  125;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy        109 NPMYNAVSNADLMDFKNLLDHLEEKMPLEDEVVPPQVLSEPNEEAGAALSPLPEVPPWTG 168
              |||||||||||||||||||||||||||||||||||||:||||||||||||||||||||
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Db          1 NPMYNAVSNADLMDFKNLLDHLEEKMPLEDEVVPPQVLSDPNEEAGAALSPLPEVPPWTG 60

Qy        169 EVSPAQRDGGALGRGPWDSSDRSALLKSKLRALLTAPRSLRRSSCFGGRMDRIGAQSGLG 228
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 EVSPAQRDGGALGRGPWDSSDRSALLKSKLRALLTAPRSLRRSSCFGGRMDRIGAQSGLG 120

Qy        229 CNSFRY 234
              ||||||
Db        121 CNSFRY 126
```

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of the '619 patent which teaches generic chimeric polypeptides comprising ANP and BNP and substitute the polypeptides comprising segments of SEQ ID NOs: 3 and 1 for sequences comprising proBNP1-108 and proANP1-126 as taught by the '838 patent for the generic ANP and BNP as taught by the '619 patent. The person of ordinary skill in the art would have been motivated to make these modifications because the '838 patent identifies the polypeptides of SEQ ID NOs:3 and 1 as proANP and pro-BNP and the '619 patent teaches chimeric proteins comprising natriuretic polypeptides such as ANP and BNP variants. Additionally, it would be obvious to one of skill in art to make a fusion protein comprising proBNP1-108 and proANP1-126 comprising SEQ ID NO: 1 and SEQ ID NO:3 taught by the '858 protein to arrive at a fusion protein of SEQ ID NO:19 of the instant invention, which comprises as amino acids 1-108 a sequence which is 100% identical to SEQ ID NO:1 of the referenced patent and as amino acids 109-234 a sequence which is 99.2% identical to SEQ ID NO:3 of the referenced patent. The one amino acid difference comprises the conservative substitution of aspartic acid for glutamic acid (both being acidic amino acids; one of skill in the art would predict that this would not change the biological activity of the fusion protein. One would be motivated to make said fusion protein because the '619 patent teaches the advantages of a therapeutic peptide comprising two natriuretic peptides. One would have a reasonable expectation of success because methods of making fusion proteins are well known in the art.

The rejection of Claims 23-26, and 50 under 35 U.S.C. 103(a) as being unpatentable over Burnett et al (the '619 patent) in view of Buechler et al (the '838

patent) as applied to claim 18 further in view of Lewicki et al (the '286 patent) and Simari (WO 00/71576, the '576 reference) is maintained for reasons of record and for reasons set forth below.

The teachings of the '619 patent and the '838 patent are outlined in detail above. The two references, individually or in combination, do not teach a polynucleotide encoding an ANP-BNP fusion protein or a polynucleotide comprising both SEQ ID NOs 9 and 12 (as recited in claim 24) or expression vectors and host cells comprising said polynucleotides.

It is noted that the '619 patent teaches chimeric proteins may be prepared by using recombinant DNA based technology (column 10, lines 37-39) and teaches expression cassettes comprising a DNA encoding chimeric natriuretic peptides (column 12, lines 14-19).

The '286 patent teaches a sequence, SEQ ID NO:3, comprising a sequence that is 100% identical to SEQ ID NO:9 of the instant invention (See alignment below and results in SCORE). The '286 patent teaches this nucleotide sequence as encoding an atrial natriuretic peptide. The reference teaches expression vectors (for example, column 6, lines 3-18, column 71, line 25) host cells (column 82, lines 46-54), and methods of making the protein of interest recombinantly (column 13, lines 38-42, and column 82, lines 46-54).

Alignment match for SEQ ID NO:9 of the instant invention

```
  Query Match             100.0%;  Score 294;  DB 2;  Length 702;
  Best Local Similarity   100.0%;  Pred. No. 1.1e-86;
  Matches  294;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy           1 AATCCCATGTACAATGCCGTGTCCAACGCAGACCTGATGGATTTCAAGAATTTGCTGGAC 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          32 AATCCCATGTACAATGCCGTGTCCAACGCAGACCTGATGGATTTCAAGAATTTGCTGGAC 91

Qy          61 CATTTGGAAGAAAAGATGCCTTTAGAAGATGAGGTCGTGCCCCCACAAGTGCTCAGTGAG 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          92 CATTTGGAAGAAAAGATGCCTTTAGAAGATGAGGTCGTGCCCCCACAAGTGCTCAGTGAG 151

Qy         121 CCGAATGAAGAAGCGGGGGCTGCTCTCAGCCCCCTCCCTGAGGTGCCTCCCTGGACCGGG 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         152 CCGAATGAAGAAGCGGGGGCTGCTCTCAGCCCCCTCCCTGAGGTGCCTCCCTGGACCGGG 211
```

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Qy        181 GAAGTCAGCCCAGCCCAGAGAGATGGAGGTGCCCTCGGGCGGGGCCCCTGGGACTCCTCT 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        212 GAAGTCAGCCCAGCCCAGAGAGATGGAGGTGCCCTCGGGCGGGGCCCCTGGGACTCCTCT 271

Qy        241 GATCGATCTGCCCTCCTAAAAAGCAAGCTGAGGGCGCTGCTCACTGCCCCTCGG 294
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        272 GATCGATCTGCCCTCCTAAAAAGCAAGCTGAGGGCGCTGCTCACTGCCCCTCGG 325
```

The '576 reference teaches a sequence that is 100% identical to SEQ ID NO:12 of the instant invention (See alignment below and results in SCORE). This sequence is described as encoding a natriuretic peptide, BNP, useful to inhibit or prevent heart failure. The reference teaches plasmids (page 7, 5th paragraph, Figure 3) and host cells expressing the protein of interest and methods of isolating recombinantly produced protein (page 7, 6th paragraph, Figure 4)

Alignment match for SEQ ID NO:12 of the instant invention

```
  Query Match             100.0%;  Score 228;  DB 4;  Length 330;
  Best Local Similarity   100.0%;  Pred. No. 1.1e-49;
  Matches  228;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 CACCCGCTGGGCAGCCCCGGTTCAGCCTCGGACTTGGAAACGTCCGGGTTACAGGAGCAG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          4 CACCCGCTGGGCAGCCCCGGTTCAGCCTCGGACTTGGAAACGTCCGGGTTACAGGAGCAG 63

Qy         61 CGCAACCATTTGCAGGGCAAACTGTCGGAGCTGCAGGTGGAGCAGACATCCCTGGAGCCC 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         64 CGCAACCATTTGCAGGGCAAACTGTCGGAGCTGCAGGTGGAGCAGACATCCCTGGAGCCC 123

Qy        121 CTCCAGGAGAGCCCCCGTCCCACAGGTGTCTGGAAGTCCCGGGAGGTAGCCACCGAGGGC 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        124 CTCCAGGAGAGCCCCCGTCCCACAGGTGTCTGGAAGTCCCGGGAGGTAGCCACCGAGGGC 183

Qy        181 ATCCGTGGGCACCGCAAAATGGTCCTCTACACCCTGCGGGCACCACGA 228
              ||||||||||||||||||||||||||||||||||||||||||||||||
Db        184 ATCCGTGGGCACCGCAAAATGGTCCTCTACACCCTGCGGGCACCACGA 231
```

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of the '619 and '838 patents which teach a chimeric protein comprising ANP and BNP and expression cassettes comprising polynuclotides encoding said chimeric or fusion proteins and substitute the polynucleotide taught by the '286 patent, SEQ ID NO:3, comprising a sequence that is 100% identical to SEQ ID NO:9 of the instant invention, encoding an ANP, for the

generic polynucleotide encoding ANP (as taught by the '619 patent) and substitute the polynucleotide sequence taught by the '576 reference comprising a sequence that is 100% identical to SEQ ID NO:12 of the instant invention, encoding a BNP for the generic polynucleotide encoding BNP (as taught by the '619 patent). The person of ordinary skill in the art would have been motivated to make these modifications because the '619 patent teaches expression cassettes comprising polynucleotides encoding chimeric natriuretic polypeptides and teaches the therapeutic advantages of such polypeptides and the '286 patent and the '576 reference teaches specific polynucleotides encoding ANP and BNP. One would anticipate success because the '619 patent teaches making such expression cassettes comprising recombinant DNA sequences.

Applicants traverse both rejections above (the rejection of Claims 18-21, 27, 49, and 51 under 35 U.S.C. 103(a) as being unpatentable over Burnett et al, the '619 patent, in view of Buechler et al (the '838 patent) and the rejection of Claims 23-26, and 50 under 35 U.S.C. 103(a) as being unpatentable over Burnett et al (the '619 patent) in view of Buechler et al (the '838 patent) as applied to claim 18 further in view of Lewicki et al (the '286 patent) and Simari (WO 00/71576, the '576 reference) (Response of 6 April 2010, page 36, 3rd paragraph, bridging page 41, 1st paragraph).

The reasons for the traversal are:

(1) None of these documents teach or suggest that a fusion polypeptide should be used in an assay, such as an immunoassay, for determining the presence of proANP and proBNP (and related proteins and peptides) in a sample. The purpose of the '619 patent was solely to provide a composition having natriuretic, rennin-suppressing, diuretic, and/or vasodilator activity, and which is useful to prevent or treat cardiovascular disorders such as congestive heart failure, and further to provide a method for inducing natriuresis, diuresis, or vasodilation in a mammal, which method is useful for treating heart failure. Further, it is not the sequences but the fusion polypeptide to be used as a diagnostic means utilizing the sequences which comprises the claimed invention.

The '619 patent teaches away from making chimeric polypeptides comprising ANP and BNP (or any other combinations of the present invention), as the focus of the '619 patent is to provide compounds having more potent natriuretic, diuretic, and/or vasodilator activity than available compounds. Accordingly, as the '619 patent would have discouraged those of skill in the art to make chimeric polypeptides including proANP and proBNP, ANP and BNP, or NT-proANP and NT- proBNP, there certainly would not have been any reason why the '619 patent would have motivated those of skill in the art to make fusion polypeptides to be used in an assay, such as an immunoassay, for determining the presence of proANP, proBNP, ANP, BNP, NT-proANP or NT-proBNP in a sample, according to the present invention.

(2) The '838 patent discloses purified BNP fragments and a method for assaying BNP and fragments thereof. This patent discloses precursor molecules of BNP, ANP, CNP, and fragments thereof, but does not include any teaching or suggestion that would guide those of skill in the art to use a fusion polypeptide, either for pharmaceutical or diagnostic purposes.

(3) The '286 patent relates to atrial peptides and analogs thereof, which are used as diuretics, natriuretics, and/or vasodilators, or as intermediates for, or modulators of, such compounds, and methods for the production and use of such compounds. An example of such a compound is atrial natriuretic/vasodilator peptide (ANVP). The '286 patent teaches that ANVP compounds can be produced by expression of recombinant DNA constructs (column 13, lines 30-41). The patent teaches the production of peptides and fragments thereof, but does not teach or suggest production of recombinant fusion polypeptides, as in the present invention. The modification concerns only the amino acid sequences of various forms of pre-proANVP, pro ANVP, and ANVP compounds (column 13, line 55-61). The '286 patent does not teach or suggest any fusion polypeptides or peptides including amino acid sequences from different natriuretic peptides, as in the present invention. The compounds produced in the '286 patent are also used to provide immunoassays for the determination of the presence or amount of ANVP compounds in sample (column 86, lines 43-46).

(4) The '576 patent application publication describes a method involving administering to a mammal at risk of, or having, a cardiovascular disease, an amount of a composition including a nucleic acid molecule, e.g., a DNA molecule which encodes BNP, DNP, or chimeras of ANP, CNP, BNP, or DNP (this statement does not disclose whether the chimera comprises different species or a chimera of the same species), effective to inhibit or prevent a cardiovascular disease, e.g., congestive heart failure (page 4, lines 8-12). This is consistent with the teachings of the '619 patent. The peptides of the '576 patent application publication should preferably have an activity similar to or greater than that of BNP, i.e., the peptide is a potent natriuretic, diuretic, vasoactive, and/or lusitropic hormone (page 4, line 33 to page 5, line 2). Accordingly, the '576 patent application publication does not propose and would not have encouraged those of skill in the art to make a fusion polypeptide to be used in an immunoassay for determining the presence of proANP and proBNP in a sample, according to the present invention.

Applicant's arguments have been fully considered but are not found to be persuasive.

In response to applicant's repeated arguments that none of the cited documents teach or suggest that a fusion polypeptide should be used in an assay, such as an immunoassay, for determining the presence of proANP and proBNP (and related proteins and peptides) in a sample, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

The claims of interest are directed to a fusion protein, a polynucleotide encoding said fusion protein, and methods of making said protein recombinantly. The claims under discussion are not claims to methods of using said fusion protein.

The '619 patent is cited for the generic teachings of the advantages of constructing fusion proteins comprising natriuretic peptides (NP) which include ANP, CNP, BNP or DNP, portions of a NP, variants of a NP (column 5, lines 27-29). While

the reference does not specifically teach constructing a proNT-ANP-pro-BNP fusion protein, the generic teachings provided by the reference would render such a construct obvious.

The '838 patent is cited for specific teachings of polypeptides which comprise sequences comprising segments that are 99.4% and 100% identical to SEQ ID NO:3 and SEQ ID NO:6, respectively (See alignment above). The '838 patent also teaches sequences comprising proBNP1-108 (SEQ ID NO:1 disclosed in the '838 patent) and a proANP1-126 (SEQ ID NO:3 disclosed in the '838 patent) (See results in SCORE); said polypeptides are recited as components of the fusion polypeptide recited in claim 19(f); the recited components comprise SEQ ID NO:19 as recited in claim 20 (See alignments below).

The combining of the generic teachings of the '619 patent (teaching construction of chimeric peptides comprising natriuretic proteins) and the specific sequences of NT-proBNP and NT-proANP, taught by the '838 patent renders the fusion polypeptide of the instant invention obvious. The fact that neither of the references teaches the use of the fusion polypeptide in an assay, such as an immunoassay, for determining the presence of proANP, proBNP, ANP, BNP, NT-proANP or NT-proBNP in a sample, is immaterial to the rejection, as the claims under consideration are directed to a fusion polypeptide, not a method of using said polypeptide.

The '619 patent teaches chimeric proteins, such as a fusion polypeptide comprising two natriuretic peptides, may be prepared by using recombinant DNA based technology and teaches expression cassettes comprising a DNA encoding chimeric natriuretic peptides; the reference thus provides a generic teaching of a polynucleotide encoding a fusion protein comprising natriuretic peptides and recombinant methods of making said peptides using said DNA. The '286 patent and the '576 reference are cited to teach specific nucleic acid sequences (SEQ ID NO:3 and SEQ ID NO:12) which are identical to the nucleic acid sequences, SEQ ID NO:9 and SEQ ID NO:12, which are claimed in the instant invention. Both the '286 patent and the '576 reference teach expression vectors, host cells, and methods of making the protein of interest recombinantly. The cited references taken as a whole render the claimed invention

obvious. The skilled artisan would be in possession of all the information necessary to construct the claimed polynucleotides encoding the claimed polypeptides and methods of making said polypeptides recombinantly.

In response to applicant's arguments against the references individually (the '286 patent and the '576 reference), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The rejection is thus maintained.

Conclusion:

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H. SHAFER whose telephone number is

(571)272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shulamith H. Shafer/
Examiner, Art Unit 1647